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MODEL STUDIES ON THE SYNTHESIS OF PSEUDOMONIC ACIDS

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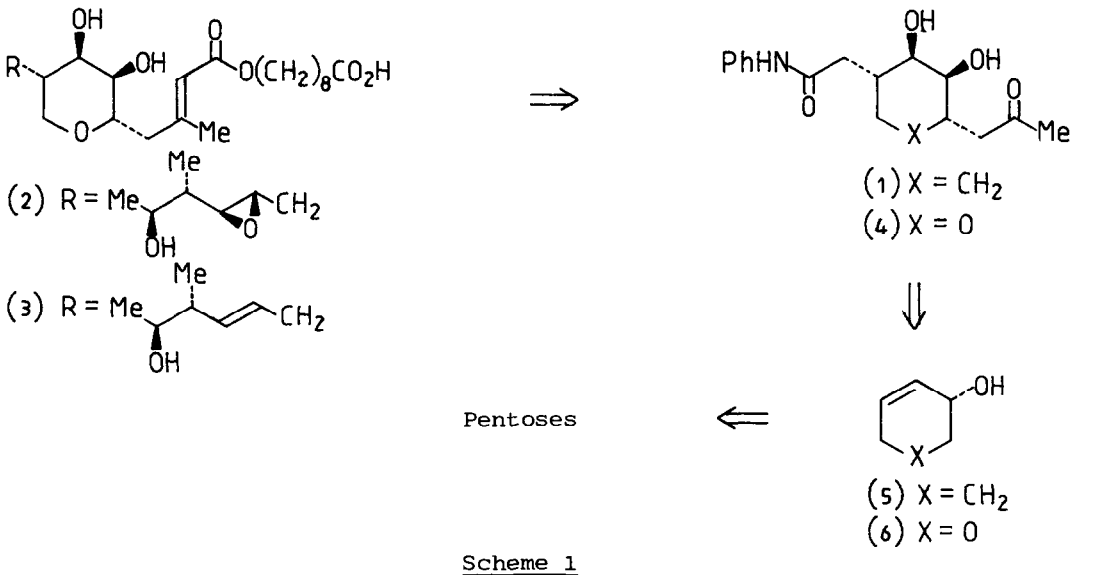
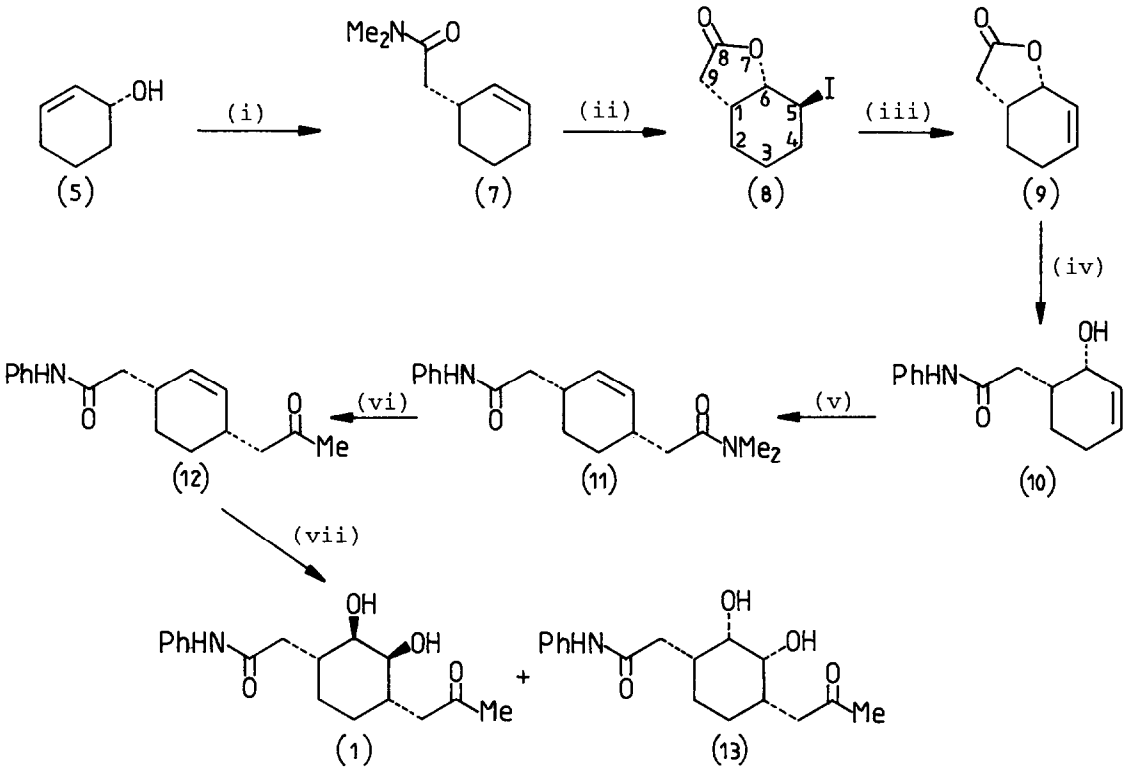
Abstract: The efficient synthesis of racemic 4α-acetonyl-2β,3β-dihydroxycyclohexane-1α-acetanilide (1) from cyclohex-2-enol demonstrates a potential strategy for the control of the stereochemistry of the four contiguous chiral carbon atoms in the pyran ring of pseudomonic acids. An intermediate containing both a secondary amide and a tertiary amide reacted with methyl lithium to give a product derived from exclusive nucleophilic attack at the tertiary amide.

Pseudomonic acids A (2) and C (3) are examples of a recently characterised group of bacterial metabolites with antimicrobial and antimycoplasmal activity.[1] Total syntheses of racemic pseudomonic acids based on oxyselenation [2,3] and acid catalysed ene[4] procedures have recently been reported. An approach (Scheme 1) to an enantiospecific synthesis of pseudomonic acids requires the synthesis of (4) which might then be elaborated by protection of the hydroxyl functions, conversion of the methyl ketone to the α,β-unsaturated ester side chain[2] followed by reduction of the secondary amide to an aldehyde[5] which could then be transformed to the natural products.[2,3] The optically active oxacyclohexenol (6) may be derived from readily available pentoses;[6] this paper illustrates an efficient route in which cyclohex-2-enol (5) is converted to racemic (1) as a model to demonstrate stereochemical control in introducing the chiral centres in (4).



Scheme 1

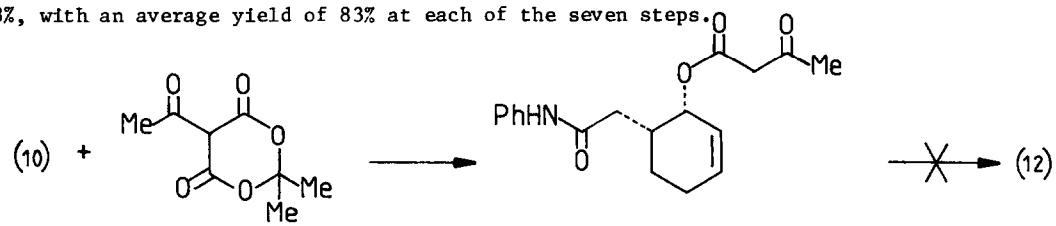


(i) $MeC(OMe)_2NMe_2$ in refluxing xylene, 18 h (ii) 3 equiv I_2 in aqueous THF at 0^o (iii) 1,5-diazabicyclo [5,4,0] undec-5-ene in refluxing benzene, 4 h (iv) PhNHLi (from aniline and n-butyl lithium) in THF at -78^o for 7 h followed by addition of aqueous NH_4Cl at -78^o (vii) N-methylmorpholine- N-oxide (1.2 equiv) and OsO_4 (catalytic amount) in acetone at room temp for 10 days, followed by flash chromatography

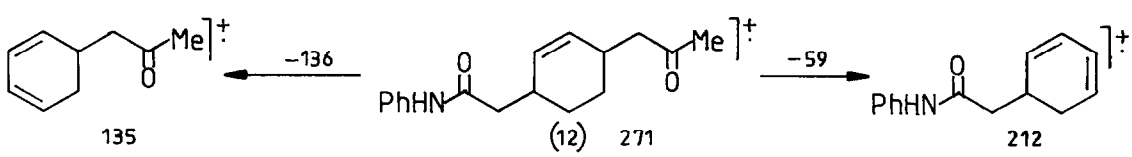
Scheme 2

The principle of the synthesis (Scheme 2) is that the stereochemistry of the two cis side chains may be controlled by Claisen rearrangements of suitable allylic alcohols. Cyclohexenol (5) was refluxed with an excess of N,N-dimethylacetamide dimethyl acetal[7] in xylene for 18 h to give the γ,δ-unsaturated tertiary amide (7) (92% yield) which on treatment with iodine in aqueous tetrahydrofuran at 0^o gave 5α-iodo-1α,6α-7-oxabicyclo-[4,3,0] nonan-8-one (8) crystallised from ethanol / hexane, m.p. 65-66° (litt.[8] 64-65°), in 82% yield. These two steps are similar to those used by Corey in the synthesis of thromboxanes derived from glucose.[9] Hydrogen iodide was eliminated from the iodolactone (8) by treatment with 1,5-diazabicyclo [5,4,0] undec-5-ene; the only hydrogen trans to the halogen is at C-4 and quantitative regiospecific elimination occurred to give the unsaturated lactone (9) which was treated without purification with the lithium salt of aniline (derived from addition of butyl lithium to a tetrahydrofuran solution of aniline) to give 2-hydroxy-3-cyclohexene-1-acetanilide (10), m.p. 140-142° (67% from the iodolactone).[10]

The Claisen rearrangement of (10) with N,N-dimethylacetamide dimethyl acetal in xylene for 4 h gave 4-(N,N-dimethylacetamido)-2-cyclohexene-1-acetanilide (11) (80% yield), m.p. 100-101° (from acetone / hexane).[10] Treatment of the bisamide (11) with 2 equiv. of methyl lithium in THF at -78° gave, after quenching at -78°, a 91% yield of 4-acetonyl-2-cyclohexene-1-acetanilide (12), m.p.116°. Initial deprotonation of the secondary amide function then allows selective nucleophilic attack at the tertiary amide carbonyl by the methyl lithium; no trace was found of products derived from attack at the alternative site. This reaction provides a novel example of chemoselectivity involving discrimination between secondary and tertiary amides. Treatment of the ketoamide (12) with N-methylmorpholine-N-oxide and a catalytic amount of osmium tetroxide[11] gave a mixture of two diastereoisomeric diols (1) and (13) which could be separated by flash chromatography.[12] Hydroxylation from the least hindered side leads to the diol (1) isolated in 75% yield, m.p. 149-150° (from acetone / hexane)[10] with the alternative diol (13) being isolated in 10% yield; this preference by osmium tetroxide for attack from this least hindered side is similar to that observed in reported pseudomonic acid syntheses[2,4] and in other situations.[13] The overall yield of (1) from cyclohexenol was 28%, with an average yield of 83% at each of the seven steps.



The feasibility of the direct conversion of the allylic alcohol (10) to the ketoamide (12) by a Carroll reaction[14] was investigated; (10) was converted quantitatively to the β-ketoester (14) by refluxing with 5-acetyl-2,2-dimethyl-1,3-dioxane-4,6-dione (15)[15] (acetylated Meldrum's acid). However, all attempts to decompose the allylic ester (14) gave complex reaction mixtures in which the desired ketoamide (12) was only present in low yields. Additional evidence for the structure of the ketoamide (12)[10] was obtained from the characteristic McClafferty rearrangements observed in the mass spectrum of (12) (Scheme 3). The presence of the α-glycol moiety in (1) was demonstrated by conversion of (1) to (12) on successive treatment with N,N-dimethylformamide dimethyl acetal followed by methyl iodide.[16]



Scheme 3

The studies outlined in schemes 1 and 2 are promising for a total synthesis of carbocyclic analogues of pseudomonic acids and provide a model system for the enantiospecific synthesis of these potentially commercially important antibiotics. The strategy is flexible and could easily be modified to produce a number of analogues in which the stereochemistry of the substituents on the rings would be readily controlled.

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